RADIATION TOXICITY: A PRACTICAL GUIDE
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Springer
To my mother’s battles with cancer that inspire me daily.
To my patients’ courage and trust that I never take for granted.
To my residents’ desire to learn.
Most of all, to Julie, Christina and Rebecca, without their support
this would not have been possible.

William Small Jr., M.D.

To the residents in our program who have kept me sharp over the years.

Gayle Woloschak, Ph.D.
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RADIATION TOXICITY: A PRACTICAL GUIDE
INTRODUCTION

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Since the discovery of radium by the Curies,¹ radiotherapy has offered incalculable benefits for cancer patients. Radiation is used in a wide variety of tumors for both curative and palliative indications. Advances in treatment delivery, diagnostic imaging, and treatment planning systems have improved tumor control and, in many cases, reduced toxicity.

A. ANTICIPATED APPROACHES TO REDUCTION OF TISSUE TOXICITY BY RADIATION

Despite these advances, radiation toxicity remains a major obstacle to effective therapy. In fact, the dose of radiotherapy that can be administered is often limited by the toxic effects of the therapy. For example, in the treatment of cervical cancer, there is good evidence of a dose–response for both the control of disease² and the risk of toxicity.³ This dose–response relationship has also been observed in prostate cancer.⁴,⁵ The ability to target radiotherapy and avoid normal tissue outside the planned radiotherapy field has been dramatically improved with the development of conformal radiotherapy and intensity-modulated radiation therapy. Future developments in these areas will no doubt further enhance the risk-benefit ratio of treatment.

Another approach that is likely to significantly reduce normal tissue toxicity is the rising use of diagnostic imaging and treatment delivery. Image-guided radiation therapies that are currently being developed will allow for simultaneous imaging of the tumor and treatment of the tumor in an individual. This will permit individualized care such that the tumor will be treated while the normal tissue will be spared as much as possible.
by actually visualizing the treatment area during the delivery of therapy. This will allow for a reduction in planning target volumes now added to the target to account for setup errors and internal organ motion.

Finally, special emphasis is being placed on understanding why some individuals have different levels of radiation toxicity than others. Once these markers have been identified, it may be possible to predict which patients are likely to have normal tissue toxicity complications from radiation exposure. For example, it is now known that expression of TGF-beta is associated with the development of lung fibrosis following radiation exposure. Characterization of the molecular basis of this response may lead to the establishment of particular genotypes or polymorphisms in the TGF-beta gene or its promoter that are predictable of a fibrotic response in a patient. Identification of such patients who are at-risk for fibrosis development and those who are not could permit dose escalation in selected patients who are not likely to develop fibrosis. The extension of this to other types of radiation toxicities and other genes might eventually lead to the profiling of each patient for susceptibilities and treatment planning based on expected radiation responses.

B. ACUTE AND LONG-TERM TOXICITY

Radiotherapy toxicity is generally separated into acute toxicity and long-term toxicity. Acute toxicity occurs during or shortly after the radiotherapy whereas long-term toxicity can manifest itself months to years after the completion of the treatment. Both acute and long-term toxicities show a dose-threshold and therefore fit into the realm of deterministic responses to radiation (as opposed to cancer development which is considered a stochastic response with no threshold).

It is generally accepted that acute toxicity occurs by direct cytotoxicity to rapidly proliferating normal tissue cells. The exact etiology behind long-term radiotherapy toxicity is somewhat a matter of controversy. The two major theories are (1) that long-term toxicity is caused by the depletion of slowly proliferating stem cells and (2) that long-term damage is related to damage to the vasculature. In actuality, the exact etiology is probably much more complex than our current level of understanding permits, involving depletion of stem cells, changes in vasculature, and alterations in cellular factors including cytokines, small molecular mediators, and others.

As advances in treatment modalities are made, more focus is shifting to a close examination of quality-of-life issues. They are particularly relevant to radiation therapy since the consequences of toxicity can be debilitating and dramatically affect bodily function. Even when disease is controlled, the short- and long-term effects of radiotherapy can have a significant impact on the quality-of-life. Patients who receive curative radiotherapy for head and neck cancers are often left with a dry mouth and consequently have great difficulty in eating and swallowing. Patients who receive pelvic radiotherapy will in many instances be left with sexual difficulties.

The purpose of this book is to provide a framework for considering normal toxicities when using radiotherapy for cancer treatment. While long-term toxicities often cannot be reversed, approaches have been developed that will permit a reasonable quality of life. Considerations to be made in treatment decisions, approaches to alleviate some
consequences of tissue toxicity, and other similar matters are all discussed in the chapters that follow. It is hoped that this will be a guide to the Radiation Oncologist, Medical Oncologist, Oncology Nurses, Radiation Therapists, and all who are involved in treatment of patients with radiation.

REFERENCES

INTRODUCTION

Neoplasms of the central nervous system (CNS) are a pathologically diverse group of benign and malignant tumors for which a variety of management strategies, including observation, surgery, radiation therapy, and/or chemotherapy, are employed. Shown in Table 1 are the usual radiation doses used to treat primary and metastatic brain and spinal cord tumors, which span a broad range of total doses and doses per fraction. Regardless of the type of CNS tumor treated, what usually limits the dose of radiation that can be utilized, and therefore what typically determines the local control and cure rate of that tumor, are the tolerance doses of the adjacent or underlying normal tissues in and around the CNS. This chapter will outline the biologic and clinical principles of CNS radiation tolerance and the management of radiation-induced CNS injury.

A. PATHOGENESIS OF RADIATION-INDUCED CNS INJURY

A1. Classical Model of Parenchymal or Vascular Target Cells

Vascular abnormalities and demyelination are the predominant histological changes seen in radiation-induced CNS injury. Classically, late delayed injury was viewed as due solely to a reduction in the number of surviving clonogens of either parenchymal, i.e., oligodendrocyte, or vascular, i.e., endothelial, target cell populations leading to white matter necrosis.
Table 1. Radiation treatment recommendations for primary central nervous system tumors

<table>
<thead>
<tr>
<th>Pathologic type</th>
<th>Gross tumor volume (GTV)</th>
<th>Clinical tumor volume</th>
<th>Total dose (Gy)/number of fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma (WHO IV) anaplastic astrocytoma (WHO III)‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial field Edema and enhancing tumor</td>
<td>GTV + 2–3 cm margin</td>
<td>46/23 or 50.4/28</td>
<td></td>
</tr>
<tr>
<td>Boost field Enhancing tumor</td>
<td>GTV + 2–2.5 cm margin</td>
<td>14/7 or 14.4/8</td>
<td></td>
</tr>
<tr>
<td>Astrocytoma (WHO II)†‡</td>
<td>Edema (and enhancing tumor if present)</td>
<td>GTV + 1–2 cm margin‡</td>
<td>50.4/28 to 59.4/33</td>
</tr>
<tr>
<td>Pilocytic Astrocytoma (WHO I) ‡</td>
<td>Enhancing tumor</td>
<td>GTV + 1–2 cm margin‡</td>
<td>50.4/28 to 59.4/33</td>
</tr>
<tr>
<td>Meningioma¶</td>
<td>Enhancing tumor</td>
<td>GTV + 1–2 cm margin‡</td>
<td>50.4/28 to 59.4/33</td>
</tr>
<tr>
<td>Medulloblastoma and anaplastic ependymoma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial volume Entire brain and spine</td>
<td>GTV + 1–2 cm margin§</td>
<td>30.6/17 to 36/24</td>
<td></td>
</tr>
<tr>
<td>Boost volume Enhancing tumor</td>
<td>GTV + 1–2 cm margin</td>
<td>19.8/11 to 25.2/14</td>
<td></td>
</tr>
<tr>
<td>Ependymoma</td>
<td>Enhancing tumor</td>
<td>GTV + 1–2 cm margin‡</td>
<td>50.4/28 to 59.4/33</td>
</tr>
</tbody>
</table>

* For anaplastic astrocytomas that are non-enhancing, plan similarly to a low-grade diffuse astrocytoma.
† Most astrocytomas (WHO I) are non-enhancing. The tumor (i.e., edema) is best seen on the T2-weighted MRI. If there is enhancing tumor, plan similarly to a glioblastoma multiforme.
‡ Reduce to a 1-cm margin after 50.4 Gy if total dose exceeds 50.4 Gy.
¶ Malignant meningiomas should be planned similarly to glioblastoma multiforme. For meningeal hemangiopericytoma, the CTV should include the GTV + 2–3 cm margin.
§ Margin at skull base should be about 1 cm, including cribiform plate. Margin on spinal canal should be 1.5–2 cm except inferior border of lower spine field, which should be at bottom of S3.

Data from Levin et al.,1 Scally et al.,2 Kun,3 and Halperin et al.4

Vascular Hypothesis

Proponents of the vascular hypothesis argue that vascular damage leads to ischemia with secondary white matter necrosis. In support of this hypothesis is the large amount of data describing radiation-induced vascular changes including vessel wall thickening, vessel dilation, and endothelial cell nuclear enlargement.6–8 Quantitative studies in the irradiated rat brain have noted time- and dose-related reductions in the number of endothelial cell nuclei and blood vessels prior to the development of necrosis.8 Further, recent boron neutron capture studies in which radiation was delivered essentially to the vasculature alone still led to the development of white matter necrosis.9 In contrast, radiation-induced necrosis has been reported in the absence of vascular changes.7 Moreover, while the vascular hypothesis argues that ischemia is responsible for white matter necrosis, the most sensitive component of the CNS to oxygen deprivation, the neuron, is located in the gray matter, a relatively radioresistant region. Thus, it seems unlikely that radiation injury is due solely to damage to the vasculature alone.
Parenchymal Hypothesis

The parenchymal hypothesis for radiation-induced CNS injury focuses on the oligodendrocyte, required for the formation of myelin sheaths. The key cell for the generation of mature oligodendrocytes is the oligodendrocyte type 2 astrocyte (O-2A) progenitor cell. Irradiation results in the loss of reproductive capacity of the O-2A progenitor cells in the rat CNS. It is hypothesized that radiation induces loss of O2-A progenitor cells, leading to a failure to replace oligodendrocytes and demyelination. However, a mechanistic link between loss of oligodendrocytes and demyelination has yet to be established. Further, while the kinetics of oligodendrocytes is consistent with the early transient demyelination seen in the early delayed reactions, it is inconsistent with the late onset of white matter necrosis. Thus, it is unlikely that loss of O2-A progenitor cells and oligodendrocytes alone can lead to late radiation injury.

Recent findings suggest that the classic model of parenchymal or vascular target cells is oversimplistic. Pathophysiological data from a variety of late responding tissues, including the CNS, indicate that the expression of radiation-induced normal tissue injury involves complex and dynamic interactions between several cell types within a particular organ. In the brain, these include not only the oligodendrocytes and endothelial cells, but also the astrocytes, microglia, and neurons. These now are viewed not as passive bystanders, merely dying as they attempt to divide, but rather as active participants in an orchestrated, yet limited, response to injury. This new paradigm offers an exciting new approach to radiation-induced normal tissue morbidity, i.e., the possibility that radiation injury can be modulated by the application of therapies directed at altering steps in the cascade of events leading to the clinical expression of normal tissue injury. Since such a cascade of events does not occur in tumors, where direct clonogenic cell kill predominates, such treatments should not negatively impact antitumor efficacy.

A2. Astrocytes

Astrocytes make up approximately 50% of the glial cell population in the brain, and are up to 10 times more numerous than neurons in the mammalian CNS. Once viewed as playing a mere supportive role in the CNS, astrocytes are now recognized as a heterogeneous class of cells with many important and diverse functions in the normal CNS. Astrocytes secrete a variety of cytokines, proteases, and growth factors that regulate the response of the vasculature, neurons, and oligodendrocyte lineage in the normal CNS. Recent data suggest that hippocampal astrocytes are capable of regulating neurogenesis by instructing the stem cells to adopt a neuronal fate. In addition, astrocytes assume a critical role in the reaction of the CNS to various forms of injury, including radiation, and are vital for the protection of endothelial cells, oligodendrocytes, and neurons from oxidative stress. In response to injury, astrocytes exhibit two common reactions, a relatively acute cellular swelling and a more chronic hypertrophy–hyperplasia. Of note, time- and dose-dependent increases in astrocyte number have been observed in the irradiated rat and mouse brain. In addition to increased cell number, an increase in GFAP staining intensity indicative of reactive astrocytes has been
observed. However, the precise pathogenic mechanism(s) impacted by the astrocyte in radiation-induced CNS injury remains unknown.

A3. Microglia

Microglia contribute approximately 10% of the total glial cell population in the adult CNS. Microglia respond to virtually any, even minor pathological event in the CNS, and in most pathological settings are assisted by infiltrating macrophages. Upon activation, they can proliferate, phagocytose, and enhance or exacerbate injury through the production of reactive oxygen species, lipid metabolites, and hydrolytic enzymes. Irradiation of the CNS has been shown to result in increased numbers of microglia in areas of tissue injury, and can occur during the latent period before the clinical expression of injury. Thus, microglia may play a role in determining the severity of radiation-induced injury in the CNS.

A4. Neurons

In view of the classic model of radiation-induced normal tissue injury, where DNA damage and loss of slowly turning over stem cell populations led to late effects, the non-proliferating neuron was thought to be radioresistant and a non-participant in radiation-induced CNS injury. Recent data documenting chronic and progressive cognitive dysfunction in both children and adults following whole brain or large field irradiation have suggested that neurons are indeed sensitive to radiation. Moreover, in vivo and in vitro experimental studies have shown radiation-induced changes in hippocampal cellular activity, synaptic efficiency and spike generation, and in neuronal gene expression. Thus, it seems likely that radiation-induced alterations in neuron function play a role in the development and progression of radiation-induced CNS injury. An additional and important component of radiation injury is the relatively recent observation that irradiation can inhibit hippocampal neurogenesis.

A5. Neural Stem Cells/Neurogenesis

The hippocampus is central to short-term declarative memory and spatial information processing. It consists of the dentate gyrus, CA3 and CA1 regions. The dentate gyrus represents a highly dynamic structure and a major site of postnatal/adult neurogenesis. Residents in the hippocampus are neural stem cells, self-renewing cells capable of generating neurons, astrocytes, and oligodendrocytes. Neurogenesis depends on the presence of a specific neurogenic microenvironment; both endothelial cells and astrocytes can promote/regulate neurogenesis. Experimental studies have indicated that brain irradiation results in increased apoptosis, decreased cell proliferation, and a decreased stem/precursor cell differentiation into neurons within the neurogenic region of the hippocampus. Rats irradiated with a single dose of 10 Gy produce only 3% of the new hippocampal neurons formed in control animals. Of note, these changes were observed after doses of radiation that failed to produce demyelination and/or white matter necrosis of the rat brain.

Further evidence demonstrating the importance of the microenvironment for successful neurogenesis comes from studies showing that non-irradiated stem cells transplanted
into the irradiated hippocampus failed to generate neurons; this may reflect a pronounced microglial inflammatory response, since neuroinflammation is a strong inhibitor of neurogenesis. In contrast to the reduction in neurogenesis, gliogenesis appears to be preserved following irradiation.

A6. Current Thinking on the Pathogenesis of Radiation-Induced CNS Injury

On the basis of the assumption that the CNS has a limited repertoire of responses to injury, the response of the CNS to other forms of insult has been used by Tofilon and Fike to model the pathogenesis of radiation-induced damage. In this model, radiation not only causes acute cell death, but also induces an intrinsic recovery/repair response in the form of specific cytokines and may initiate secondary reactive processes that result in the generation of a persistent oxidative stress and/or chronic inflammation.

A7. Laboratory Studies of Therapeutic Interventions for Radiation-Induced CNS Injury

As noted earlier, radiation-induced CNS injury has been well characterized in terms of histological criteria as well as radiobiological parameters. In contrast, details of the molecular, cellular, and biochemical processes responsible for the expression and progression of radiation-induced CNS injury currently are limited. Thus, the rational application of interventional procedures directed at reducing the severity of late radiation injury is currently problematic. To date, several pragmatic but nonspecific approaches have been used.

Intrathecal administration of the classic radioprotector WR-2721 (Amifostine) before spinal cord irradiation resulted in a dose-modifying factor of 1.3 and a prolongation of median latency to myelopathy by 63% at the ED50. Fike et al. observed that the polyamine synthesis inhibitor α-difluoromethylornithine reduced the volume of radionecrosis and contrast enhancement in the irradiated dog brain; a delayed increase in microglia was also noted. Hornsey et al. hypothesized that treating rats with the iron-chelating agent desferrioxamine would reduce hydroxyl-mediated reperfusion-related injury in the irradiated spinal cord. Rats were fed a low-iron diet from 85 days after local spinal cord irradiation and received desferrioxamine (30 mg in 0.3 mL, sc, 3 times/week) from day 120, the time at which changes in vascular permeability were noted. The onset of ataxia due to white matter necrosis was delayed and the incidence of lesions was reduced after single doses of 25 and 27 Gy. Dexamethasone also delayed the development of radiation-induced ataxia along with a reduction in regional capillary permeability. In contrast, indomethacin did not appear to affect any of these endpoints. In the pig, administration of the polyunsaturated fatty acids γ-linolenic acid (GLA; 18C:3n-6) and eicosapentaenoic acid (EPA; 20C:5n-3), starting the day after spinal cord irradiation, was associated with a reduced incidence of paralysis, from 80% down to 20%. More recently, El-Agamawi et al. reported that GLA significantly reduced the onset of paralysis following spinal cord irradiation in 5-week-old rats. Prophylactic hyperbaric oxygen (HBO) has also been used to try and prevent radiation-induced myelopathy in a rat model. Using a dose of 65 Gy in 10 fractions with or without 30 HBO treatments following the irradiation, Sminia et al. did not demonstrate any
preventive value to HBO. In fact, there was a “tendency toward radiosensitization” in the HBO-treated rats.\textsuperscript{49} Administration of ramipril, an angiotensin converting enzyme inhibitor, from 2 weeks after stereotactic irradiation with a single dose of 30 Gy, until 6 months postirradiation, was associated with a reduction in the severity of optic neuropathy.\textsuperscript{50}

Attempts have been made to rectify the radiation-induced decrease in neurogenesis. Rezvani et al.\textsuperscript{51} transplanted neural stem cells 90 days after irradiation of the rat spinal cord with a single dose of 22 Gy. While 100\% of the irradiated rats treated with saline exhibited paralysis within 167 days of irradiation, the paralysis-free survival rate of rats treated with neural stem cells was approximately 34\% at 183 days. These findings are somewhat controversial; non-irradiated stem cells transplanted into the irradiated rat hippocampus failed to generate neurons, although gliogenesis was spared.\textsuperscript{40} Preliminary data suggest that IGF-1 may show efficacy in not only preventing radiation myelopathy in adult rats,\textsuperscript{52} but also in ameliorating the radiation-induced cognitive dysfunction observed in the rat following whole brain irradiation.\textsuperscript{53}

B. CLINICAL ASPECTS OF CNS RADIATION TOLERANCE

The radiation tolerance of the CNS is dependent on a number of factors, including total dose, dose per fraction, total time, volume, host factors, radiation quality (linear energy transfer), and adjunctive therapies. Table 2 defines the role of these factors in radiation tolerance and injury to the brain, as well as ways they might be modified to increase tolerance (i.e., reduce injury).\textsuperscript{54,55}

Table 3 shows partial and whole organ tolerance doses for the brain and spinal cord, and includes doses predicted to result in a 5\% and 50\% probability of injury 5 years following treatment with radiation (TD 5/5 and TD 50/5, respectively).\textsuperscript{56,57} These values are derived from mathematical models of brain and spinal cord tolerance based on the clinical data describing the instances of radiation injury and the total doses and fraction sizes at which they occurred. None of the mathematical models account for the factors listed in Table 2, nor do they adequately predict radiation tolerance or injury.

<table>
<thead>
<tr>
<th>Factor\textsuperscript{*}</th>
<th>Factors for increased risk of injury</th>
<th>Tolerance increased by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dose</td>
<td>Higher total dose</td>
<td>Decreasing total dose, hyperfractionation\textsuperscript{†}, radiosensitizers</td>
</tr>
<tr>
<td>Dose per fraction</td>
<td>Dose per fraction &gt;180–200 cGy</td>
<td>Decreasing dose/fraction to ≤ 180–200 cGy</td>
</tr>
<tr>
<td>Volume</td>
<td>Increased volume, e.g.,</td>
<td>Decreasing volume, e.g., partial-organ radiation</td>
</tr>
<tr>
<td>Host factors</td>
<td>Medical illness, e.g., hypertension, diabetes</td>
<td>Unknown, possibly radioprotectors</td>
</tr>
<tr>
<td>Beam quality</td>
<td>High LET radiation beams, e.g., neutrons</td>
<td>Low LET beams, e.g., photons</td>
</tr>
<tr>
<td>Adjunctive therapy</td>
<td>Concomitant use of CNS toxic drugs, e.g., methotrexate</td>
<td>Avoid concomitant use of CNS toxic</td>
</tr>
</tbody>
</table>

\textsuperscript{*}Total time is not a major determinant of normal CNS tissue tolerance.

\textsuperscript{†}Defined as multiple daily fractions, usually two with doses per fraction of ≤180–200 cGy, usually 100–120 cGy, separated by 4–8 hours, to total doses higher than those given with “standard” fractionation.

Data from Leibel and Sheline\textsuperscript{54} and Schultheiss et al.\textsuperscript{55}